PETITION FOR EXTENSION OF TIME

Applicants hereby request a two-month extension of time extending the time for a response from November 30, 1995, up to and including January 30, 1996. The Assistant Commissioner is hereby authorized to charge the required $380.00 extension fee to Deposit Account No. 23-1703. Any additional fees due in connection with this request should likewise be charged.

Please amend the application as follows:

In the Claims:

Please amend the claims as follows:

1. (thrice amended) A medicament containing as active ingredients effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide.

REMARKS

Claims 1, 2, 7 and 14-23 are pending in the application. Claim 1 has been amended to better define the subject matter regarded as the invention.

Claims 1, 2, 7 and 14-23 have been rejected under 35 U.S.C. § 103 as being obvious for the reasons of record and as previously applied to claims 1-3 and 5-13. The Examiner

acknowledges that Dr. Trofast's Declaration, submitted June 9, 1995, sets forth data demonstrating the unexpected properties of Applicants' invention; however, the Examiner also contends that Applicants' showing is not commensurate in scope with the claims. The Examiner opines that the broadest allowable claim supported by the data would be one which recites that the amount of the formoterol-budesonide combination is an effective amount and that the ratio of formoterol to budesonide ranges from 1:1 to 1:20.

In response to the rejection, Applicants submit herewith for the Examiner's consideration a second Declaration under 37 C.F.R. § 1.132 of Dr. Trofast. The original signed copy of the Declaration, without the exhibits, is being transmitted concurrently by first class mail. The new Declaration sets forth additional data obtained from the same Sephadex-induced edema model according to the protocols set forth in the earlier Declaration. In the new experiments, the antiasthmatic effect of formoterol- budesonide combinations in a molar ratio of 1:60 was tested. As was seen with ratios previously tested, the effect of a 1:60 formoterol budesonide ratio (69% inhibition) was seen unquestionably to be significant and far greater than the sum of the individual effects of the components.

The Examiner asserts that the showing must be commensurate in scope with the claims and cites Perrin v.Kalk, 1 U.S.P.Q.2d 1881 (BPAI 1986) as support for this ground of rejection. Applicants note that the judgment in Perrin v. Kalk was essentially that comparison of a single compound of a claimed genus encompassing thousands of compounds with a prior art compound is not sufficient to support the scope of the claimed genus.

The instant situation is nothing like that of Perrin v. Kalk. Even prior to the submission of the concurrent Declaration, Applicants had demonstrated the unexpected properties of a number of ratios within the claimed range of ratios. With the new data set forth in the accompanying Declaration, Applicants have now demonstrated the nonobviousness of formoterol- budesonide ratios ranging from 1:1 to 1:60.

The Examiner acknowledges that the probative value of data can be extended to support a broader claimed range but only when it is possible to "ascertain a trend" and cites In re Clemens, et al., 206 U.S.P.Q. 289 (CCPA 1980). The Examiner cites the "unpredictable nature of synergism" and asserts that a trend cannot be ascertained with regard to Applicants' showing in the instant application. In the application which was the subject of In re Clemens, Applicants provided data showing unexpected properties of

their resin over a prior art resin above a certain temperature but were claiming a temperature range which included temperatures at which the prior art resin was known to have desirable properties.

The situation in the instant application is not at all the same. In the instant application, Applicants are not obliged to demonstrate the unexpected properties of the claimed compositions over any prior art compositions, but only to demonstrate that the properties of combinations of the active ingredients are greater than the sum of the properties of the individual components at ratios representative of the range of ratios claimed.

In fact, In re Clemens cites In re Kollman, 201 U.S.P.Q. 193 (CCPA 1979) as providing the criterion for determination of what constitutes a "trend" in data. In In re Kollman, it was seen that the effectiveness of the claimed compositions increased as the ratios of components approached the contested region of the claimed range of ratios and yet still far outstripped the additive total of expected effectiveness, and this was judged to support the probative value of a given range of data for extension to prove the nonobviousness of a broader claimed range.

Applicants' showing in the instant application clearly fulfills the criterion of In re Kollman as to the establishment of a trend and the probative value of a given

range of data. As can be seen from the data in Dr. Trofast's earlier and concurrent Declarations, all tested ratios of formoterol to budesonide, ranging from 1:1 to 1:60, demonstrate unexpected potency, and the potency continues to increase with decreasing formoterol-to-budesonide ratio. As pointed out in the concurrent Declaration, given the heightened sensitivity of the rat to budesonide, one must consider that one will reach a point when the effect of budesonide alone is so strong as to mask any synergistic effect of a formoterol-budesonide combination. One can achieve a maximum of 100% inhibition, and the previously tested 1:20 ratio, providing 66% inhibition, approaches that limit; yet the newly tested 1:60 ratio, showing 69% inhibition, demonstrates not only synergy but an increased inhibition over that of the lowest previously tested ratio.

Further with regard to the phenomenon of heightened sensitivity in the rat, it was pointed out in Dr. Trofast's first Declaration and is reemphasized and further supported in the concurrent Declaration that one of skill in the art would expect from 3 to 10 times greater sensitivity to glucocorticoids in rats as compared to man. Therefore, the effect of administration of a 1:60 molar ratio of formoterol to budesonide in the rat can be taken to be reflective of a molar ratio of 1:200 or lower in a human subject.

By extension, the combined test data in the two Trofast Declarations are directly reflective of a ratio range in humans which is much broader than that from 1:1 to 1:60.

More than that, the trend to which the Examiner alludes has clearly been established, and one skilled in the art would understand that these data support a finding of synergy for formoterol-budesonide combinations over any contemplated range of therapeutic administration. Applicants' broader claims reciting "effective amounts," together with narrower claims reciting preferred embodiments, are thus appropriate and allowable.

The data on their own are commensurate in scope with the claims. Even if this were not the case, the data establish a trend and have a probative value which can be extended to prove the nonobviousness of a considerably broader claimed range. Finally, the data obtained in the rat model are actually reflective of a considerably broader ratio of administration in humans.

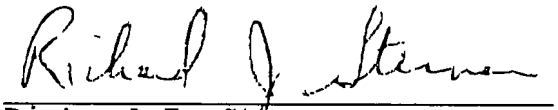
In light of the above, the claimed subject matter is nonobvious, and the present scope of the claims is enabled. Reconsideration and allowance of pending claims 1, 2, 7 and 14-23 are respectfully requested.

Should any other matters require consideration prior to allowance of the application, it is requested that the Examiner contact the undersigned.

The Assistant Commissioner is hereby authorized to charge any fees due in connection with this communication to Deposit Account No. 23-1703.

Dated: January 9, 1996

Respectfully submitted,



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Enclosure